

Guidance for Industry

GAMMA IRRADIATION OF BLOOD AND BLOOD COMPONENTS: A PILOT PROGRAM FOR LICENSING

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only. _

Comments and suggestions regarding this **draft** document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the **draft** guidance.

Submit all comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5600 Fishers La., rrm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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For questions on the content of this **draft** document contact Mary Ann Denham, Consumer Safety Officer, Division of Blood Applications, (301) 827-3543.

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GUIDANCE FOR INDUSTRY¹

GAMMA IRRADIATION OF BLOOD AND BLOOD COMPONENTS:

A PILOT PROGRAM FOR LICENSING

I. PURPOSE

This document provides Food and Drug Administration (FDA) acceptable criteria for the gamma irradiation of blood and blood components for transfusion. FDA believes that the procedures recommended in this document reflect practices currently in use by most manufacturers and represent the prevailing industry standard.

II. INTRODUCTION

Pursuant to section 351 of the Public Health Service Act (42 U.S.C. 262 et seq.), all biological products, including blood and blood components, introduced or delivered for introduction into interstate commerce must be licensed by FDA. Traditionally, manufacturers of blood and blood components have applied for an establishment license and product licenses for Whole Blood, Red Blood Cells, Plasma, Platelets, Cryoprecipitated AHF, Source Plasma and Source Leukocytes. Licenses have been issued by FDA, Center for Biologics Evaluation and Research (CBER) only after a license application review and prelicense inspection determined that the establishment conformed to standards prescribed in the regulations and that the products manufactured by the establishment were manufactured in a manner to assure safety, purity, and potency. Any changes in manufacturing methods or intended use of products have required submission of supplements to each application. More recently, FDA has streamlined the biologics license application process by initiating a process to eliminate the establishment license application (ELA) and will soon consolidate the product application into a single biologics license application (BLA) (July 31, 1998, 63 FR 40858). Reporting changes to an approved application have also been modified by the new requirements of 21 CFR 601.12-Changes to an Approved Application (July 24, 1997; 62 FR 39890). However, even with the efficiencies of the BLA and Title 21 CFR 601.12 revisions, the process of the BLA, supplement preparation, and FDA review is resource intensive to industry and FDA.

¹ This guidance has been prepared by the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents FDA's current thinking on gamma irradiation of blood and blood components intended for transfusion. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

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With this in mind, FDA is proposing a pilot program that would allow a manufacturer to **self-certify** conformance to specific criteria as a substitute for CBER review of information submitted in a BLA supplement. FDA has chosen for this pilot, the gamma irradiation of blood and blood components. FDA believes that most manufacturers of gamma irradiated blood and blood components have a positive record of product safety, purity, and potency, and a high level of adherence to current Good Manufacturing Practice (**cGMP**) regulations [21 CFR Parts 606, 210, and 211]. This action is part of FDA's continuing effort to achieve the objectives of the President's "Reinventing Government" initiatives and is intended to reduce unnecessary burdens for **industry** without diminishing public health protection.

The pilot program would allow a manufacturer of gamma irradiated blood components to submit a self-certification statement as a supplement to the approved **biologics** license **application**, together with a written request for an exception from filing a detailed supplement. That is, instead of submitting a BLA supplement with supporting operating procedures and data derived from validation and quality control testing, the manufacturer would submit a BLA (**FDA Form 356h**), a self-certification statement that provides that the manufacturer is in compliance with **all** applicable FDA regulations [i.e., 21 CFR Parts 600-680, 210 and 211], and meets the criteria for gamma irradiated blood and blood components in this guidance document, and a written request to the Director, **CBER**, for an exception pursuant to 21 **CFR** 640.120, from the requirement set forth in 2] CFR 601.12(b)(3) to submit a detailed supplement. The applicant **should** complete page 1 of the FDA Form 356h consistent with the instructions in the **draft** FDA guidance ' document dated July 1998, "Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for **Transfusion** or for Further Manufacture and For the Completion of the FDA Form 356h, Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" (63 FR 37402). On page 2 of the FDA Form 356h, the applicant should indicate items #2-Labeling and #19-Other (self-certification statement for pilot program) on the checklist and complete the certification/signature section. The self-certification statement would indicate that the manufacturer is ready for inspection. As a **further** streamlining effort and incentive to participate in the **program**, FDA will attempt to **perform a pre-approval** inspection of the manufacturer's manufacturing site(s) within 90 days of receipt of the self-certification statement. The applicant should also forward a written request pursuant to 21 CFR 640.120 for **an** exception from the requirement set forth in 21 CFR 601.12(b)(3) to file a detailed supplement. The request should reference the applicant's participation in the pilot program.

If there is adequate interest in the pilot program, FDA will announce the initiation of the program in the **Federal Register**, and conduct the program for approximately one year. At the end of the pilot **program**, FDA will evaluate the program in terms of product safety, purity and potency and also resource efficiency and effectiveness. If the program seems to be efficient and effective without compromising product safety, purity, and potency, FDA intends to allow manufacturers

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of gamma irradiated blood and blood components to continue to pursue the self-certification alternative. FDA may also extend the self-certification process to other blood and blood components. Regardless of the results of the pilot program (if initiated), manufacturers of gamma irradiated blood and blood components will always be able to submit a detailed BLA supplement and receive a complete review of the application by FDA.

This draft document should be reviewed and considered in connection with the notice announcing the pilot program for Gamma Irradiation of Blood and Blood Components. [As of December 8, 1998, pending for publication in the **Federal Register**.] In this guidance document, FDA proposes to establish an alternative process that, if adopted in its entirety by a manufacturer, eliminates the need to submit detailed information to FDA to be reviewed prior to inspecting the manufacturing facility. Although FDA recognizes that there may be acceptable alternatives in the manufacture of irradiated blood and blood components, the agency will accept only the conditions prescribed in this document as acceptable for the purposes of participation in the pilot program. Other conditions of manufacture maybe licensed by **FDA**, but only in the context of a complete license application review.

This draft guidance is being distributed for comment purposes only and is not intended for implementation. CBER intends to revise this document based on comments received on the pilot program, and the draft guidance document.

III. BACKGROUND

The reason for irradiating blood and blood components is to prevent graft-versus-host disease (GVHD) by decreasing the number of viable T lymphocytes. **GVHD** occurs when viable T lymphocytes in **transfused** blood or blood components **engraft**, multiply, and react against the tissues of the recipient. **GVHD** maybe seen when blood components are transfused to **immunocompromised** recipients, such as bone marrow transplant patients, patients with malignancies receiving aggressive chemotherapy, and persons with congenital immune deficiency syndromes.

There are reports of **GVHD** occurring in apparently non-immunocompromised recipients following transfusion of blood donated by family members.¹⁴ **GVHD** may occur more frequently in cases of family member transfusions than in random donor transfusions because **family** members are more likely to share the same **histocompatibility** locus antigen (**HLA**) **haplotypes** than people in the population at large. In many of these cases, it was found that the donors were **HLA homozygous** for one of the recipient's **haplotypes**. In such situations, the recipient's lymphocytes do not recognize HLA antigens on the donor's lymphocytes as **foreign**, and the donor's lymphocytes can survive indefinitely and may react immunologically against the recipient's tissue, which express a **heterologous haplotype**.

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Blood and blood components implicated in cases of transfusion associated (TA)-GVHD include: Platelets; Platelets, **Pheresis**; **Granulocytes**, **Pheresis**; Whole Blood; and Red Blood Cells. Methods of producing leukocyte-reduced blood and blood components (including washing, filtration, and **centrifugation**) reduce the number of viable T lymphocytes, but may not decrease the risk of TA-GVHD as effectively as gamma irradiation.⁵⁻⁷

Iv. **SPECIFIC CRITERIA**

A. IRRADIATION PERFORMED BY THE APPLICANT BLOOD ESTABLISHMENT

When irradiation is performed by a blood establishment in its own facility or in another department of the same facility, i.e., radiation therapy, GMP regulations as outlined in Title 21, Code of Federal **Regulations(CFR)**, Parts 606, 210, and 211, must be followed.

1. Standard Operating Procedures (SOP)

SOPS must be developed, approved, implemented, and maintained in _ the following areas [21 CFR 606.100(b), 21 1].

a. Equipment and Maintenance

- 1) Only those blood irradiators that have been cleared through the 510(k) process [21 USC 360(k)] by the Center for Devices and Radiological Health, Food and Drug **Administration**, and properly validated for irradiation of blood and blood components, will be acceptable for this pilot program.
- 2) Manufacturer's instructions should be incorporated into the SOP and must be followed [21 CFR 606.65 and 606.100].
- 3) All equipment used in the production of irradiated blood components should be qualified for such use. **Qualification**, including **installation**, operation and **performance**, should be completed prior to validation and as necessary during the life of the equipment. Qualification should also include measuring the amount of radiation delivered to the product.

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- 4) All equipment used in the production of irradiated blood components must be calibrated in accordance with the manufacturer's instructions or comparable procedure [21 CFR 606.60(a)]. Calibration of equipment must be performed according to a predetermined and routine schedule as specified in an SOP [21 CFR 606.100 (b)(1 5)].

b. Dosage and Time to Deliver Dose

- 1) The dose of irradiation delivered should be 2500 cGy targeted to the central portion of the container and the minimum dose should be 1500 cGy at any other point.
- 2) The time required to deliver the dose should be based on the radiation intensity of the source. The decay of the source should be calculated according to manufacturer's instructions. FDA currently recommends recalibration of the source annually for **Cesium- 137** and semi-annually for Cobalt-60, The procedure for calculating decay, included in the operator's manual for the irradiator, may be referenced in the SOP.
- 3) The SOP should indicate the maximum number of units of blood or blood components that can be irradiated at one time. This constitutes a batch and maybe dictated by the device manufacturer's procedure and based on the firm's validation data.
- 4) At no time should the total irradiation dose exceed 5000 cGy to any portion of the container.

c. Indicators

An irradiation indicator should be used with each irradiated batch. There should be procedures for the quality control of the indicator system in use which should include, but not be limited to, storage of indicator, verification that the indicator has not been exposed to unacceptable temperatures, and explanation of expected results for each new lot (comparison with the old lot) and corrective action.

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There must be documentation of such quality control [21 CFR 606. 160].

d. Labeling

- 1) The immediate container of blood and blood components that has been irradiated should be permanently labeled as irradiated. Applicants must submit labels to CBER for review and approval [21 CFR 606. 160]. (2,3)
- 2) Only FDA approved product names “and codes shall be used [21 CFR 606. 121(c)(1)].

e. Dating Period

- 1) The dating period for red blood cell products should not be more than 28 days from the date of **irradiation**, but should not exceed the dating period of the original product.
- 2) The dating period for platelet and plasma products need “ not change after irradiation since they are not adversely **affected** by irradiation.

2. Quality Assurance (QA)

For the pilot program, the following procedures should be used to **validate** the irradiation system.

a. Process Validation

- 1) Blood component irradiation must be validated [21 CFR 211. 100]. Validation should include measuring the amount of irradiation absorbed by the product, including all load configurations, using predetermined parameters.

2 Tie-tags and indicators are not appropriate labels for irradiated blood and blood **components** since the product **label**, which includes the word “**Irradiated**,” should be a permanent label attached directly to the product.

3 The special message label, i.e. the purple label referenced in the Uniform **Guidelines** for the Labeling of Blood and Blood Components 1985, is no longer an appropriate **label** because the current product labels now must include the word “Irradiated.”

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- 2) Validation should be performed on a **fully** loaded canister to obtain the maximum and minimum dose of irradiation to which the blood and blood components will be subjected.
 - 3) Validation should be performed using a dosimetry system.
 - The dosimetry system should provide a dose map. In the scientific literature there are discussions regarding dosimetry systems in current **use**.⁸
 - The medium for **dosimetry** should **be** one that closely resembles blood, e.g., water or some types of **acrylic**.⁹
 - The dose map should be reviewed and retained in the records.
 - A test run should be **performed** three (3) times on load configurations using blood products to **verify** that the validation parameters are met.
 - The process should monitor the temperature of the blood products during the irradiation procedure to ensure that the time the blood products spend out of a controlled environment is limited to prevent the warming of the red cell products above 10°C and platelet products above **24°C**.
- b. Quality Control (QC)
- 1) Equipment used in the production of irradiated blood components must have routine quality control testing performed on a scheduled basis [21 **CFR** 606.140(b)]. The **QC** must, at a minimum, follow the manufacturer's instructions [21 **CFR** 606.60(a)].
 - 2) Each day of use

The timer on the irradiator should be compared visually against the back-up timer if available or with a certified

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stopwatch if there is not a back-up timer, and the results of the comparison should be documented.

If a moving turntable is part of the equipment, a visual check of the turntable should be made to determine that it is rotating. This should be documented.

3) Monthly

If the irradiator in use has a backup timer, the two timers should be checked monthly using a certified National Institute of Standards and Technology (NIST) stop watch. This should be documented.

4) Periodically

Although blood irradiators are considered **safe**, facilities should periodically check for radiation leakage. This can be done with a Geiger counter or using a wipe test.⁸⁻⁹

3. **Recordkeeping**

Records must be maintained according to 21 CFR 606.160.

- 1) Records must document the significant steps in the irradiation of each component including identification number and quality assurance personnel, and these records should be reviewed by quality assurance.
- 2) The duration of the irradiation procedure must be recorded.
- 3) The dose of irradiation must be recorded for each batch.
- 4) The identity of the person performing the irradiation must be recorded.
- 5) The date, time, and site of the irradiation must be recorded.

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B. IRRADIATION PERFORMED BY AN OUTSIDE CONTRACTOR

1. Standard Operating Procedure

- a. The blood establishment is responsible for ensuring that SOPS are in place and the manufacturing steps are **performed** according to the blood establishment's specifications for both the blood establishments and the outside contractor. The blood establishment should have a mechanism in place for ensuring that the contractor is meeting the requirements of the regulations.
- b. The SOPS and records of both the blood establishment and the outside contractor should be consistent with Section A of this document.
- c. If irradiation of blood and blood components is **performed** by an outside contractor, each party must have SOPS**specifying** those steps performed by the blood establishment as well as those performed by the outside contractor [21 **CFR** 606.100(b)].

2. Registration and Regulatory Responsibilities

Since the contract facility is performing a manufacturing step, it must be registered with FDA [21 **CFR** 607.7 (a)]. The applicant should **identify** and have evidence of registration of the contractor. All contract facilities are subject to FDA inspection and all applicable **cGMP** regulations [21 **CFR** 600.20,21 **CFR**, **Parts** 606,210, and 21 1].

3. Agreement

There should be a written agreement between the applicant and the outside contractor that outlines the responsibilities of each party to the agreement.

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V. GLOSSARY

Applicant: Any legal person or entity who has submitted an application to manufacture a product subject to licensure under section 351 of the Public Health Service Act [42 USC 262].

Contractor: Any person or entity, not the applicant, who performs part or all of the manufacturing of the licensed product at the request of the applicant. The applicant assures the contractor's compliance with the applicable product and establishment standards. Both the applicant and the contractor are legally responsible for the work performed by the contractor.

Component: That part of a single-donor unit of blood separated by physical or mechanical means [21 CFR 606.3(c)].

CFR: Code of Federal Regulations.

Current Good Manufacturing Practice (cGMP): Methods used in, and the facilities or controls used for, the manufacture, processing, packing, or holding of a drug including, but not limited to, blood components, to assure that such product meets the requirements of the Federal Food, Drug and Cosmetic Act as to the safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess [See FD&C Act, Sec. 501(a)(2)(B)]. cGMP ensures products are consistently manufactured and controlled by quality standards appropriate to their intended use. It encompasses both manufacturing and quality control/quality assurance procedures.

Dose Map: Measures the delivery of radiation within a simulated blood component or over an area in which the blood component is placed.

Dosimetry: A system used for determining absorbed dose, consisting of dosimeters, measurement instruments and their associated reference standards, and procedures for the system's use.

Validation: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Qualification: Establishing confidence that process equipment, reagents, and ancillary systems are capable of consistently operating within established limits and tolerances. Process performance qualification is intended to establish confidence that the process is effective and reproducible.

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Quality Assurance (QA) Program: An organization's comprehensive system for manufacturing safe, effective, and quality products according to regulatory standards. This program includes preventing, detecting, and correcting deficiencies that may compromise product quality.

Quality Control/Assurance (QC/QA) unit: One or more individuals designated by, and reporting directly to, management with defined authority and responsibility to assure that all quality assurance policies **are** carried out in the organization.

Quality Control (QC): A component of a QA program that includes the activities and controls used to determine the accuracy and reliability of the establishment's personnel, equipment, reagents, and operations in the manufacturing of blood components including testing and product release.

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